Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Deep Brain Stimulation of the Nucleus Basalis of Meynert for Parkinson's Disease Dementia: A 36 Months Follow Up Study

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ABSTRACT: Background: Degeneration of the nucleus basalis of Meynert (NBM) and cortical cholinergic dysfunction are hallmarks of Parkinson's disease dementia (PDD). There is no effective therapy for PDD. Deep brain stimulation of the NBM (NBM-DBS) has been trialed as a potential treatment.
Objective: Our primary aim was to evaluate the sustained tolerability of NBM-DBS in PDD, and its impact on global cognition, behavioral symptoms, quality of life and caregiver burden and distress. Second, we aimed to determine whether baseline measures of arousal, alertness, and attention were predictive of the three year response to NBM-DBS in PDD patients.
Methods: Five of the six PDD patients who completed the baseline assessment participated in a 3 year follow up assessment. We assessed the participants after three years of NBM-DBS on the Mini Mental State Examination, Dementia Rating Scale-2, Blessed Dementia Rating Scale, Neuropsychiatric Inventory, and the SF36.
Results: The five patients showed varying trajectories of cognitive decline, with two showing a slower progression over the three-year follow-up period. A slower progression of decline on global cognition was associated with higher baseline accuracy on the Posner covert orienting of attention test, and less daytime sleepiness.
Conclusions: Whether slower progression of cognitive decline in two patients was in any way related to individual variability in responsiveness to NBM-DBS requires confirmation in a larger series including an unoperated PDD control group. Higher accuracy in covertly orienting attention and better sleep quality at baseline were associated with better cognitive outcomes at 36 months assessment. These results require validation in future studies with larger samples.

Approximately 10 million people worldwide suffer from Parkinson's Disease (PD). Mild cognitive impairments are detectable from the early stages of the disease and may predict conversion to Parkinson's disease dementia (PDD),[1] which increases with disease duration and ultimately affects over 70% of PD patients.[2] PDD reduces the quality of life and increases caregiver burden and distress.[3]

Cognitive decline in PDD is associated with marked cerebral cholinergic dysfunction, which underlies impairments in attention, executive and visuospatial functions, and memory.[4] The nucleus basalis of Meynert (NBM) provides the major source of cholinergic innervation to the cortex,[5,6] and NBM degeneration plays a key role in the pathogenesis of PDD.[7–9]

There is no cure for PDD. Standard medical treatments include acetylcholinesterase inhibitors that upregulate cortical acetylcholine (ACh) levels, but they are only partially effective in managing the cognitive symptoms.[10] There is, therefore, an unmet clinical need to find new therapeutic interventions to

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slow down the progression of dementia. NBM deep brain stimulation (NBM-DBS) in an attempt to increase cortical ACh levels, and thereby improve cognitive symptomatology, has been considered as a potential therapeutic option to improve cognitive symptoms in PDD, as well as in Alzheimer's disease (AD).[6,11–14]

The rationale for choosing NBM as a target for DBS comes from animal research showing that the NBM is strongly associated with arousal, sleep/wake regulation, alertness, and focused attention, by controlling cortical ACh levels.[6] In particular, stimulation of the NBM in rodents enhances cortical ACh release, which promotes a wakeful and alert state,[15,16] whereas lesions to rodent NBM result in a reduction of alertness or a comatose state.[17,18] Furthermore, NBM stimulation has been shown to modulate neocortical excitability, thus inducing synaptic plasticity and learning.[16,19,20] This evidence suggests that NBM-DBS in humans might be expected to impact residual cholinergic neurons to boost cortical ACh, thereby restoring levels of behavioral alertness/attention, and in doing so improving cognitive functioning.

Growing evidence indicates that arousal disturbances occur very early in the course of neurodegenerative disorders, and not only serve as indicators of disease onset but may also contribute directly to pathogenesis.[21] Indeed, excessive daytime sleepiness in dementia patients has long been implicated in causing impaired vigilance, alertness, and attention, which is manifested objectively by slowing of reaction times and decrease of attentional and general cognitive performance.[22] Consistent with this, disrupted sleep, shortened REM sleep, and excessive daytime sleepiness, all of which affect vigilance and alertness, as well as attentional and cognitive abilities, are common symptoms in PDD.[22,23] Furthermore, a recent study showed that excessive daytime sleepiness in PD patients is indicative of a more severe loss of basal forebrain cholinergic integrity.[24]

We previously conducted a randomized, double-blind sham-controlled cross-over trial of NBM-DBS in 6 patients with PDD.[12] In the current study, our primary objective was to complete a 3-year (36 months) longitudinal follow up to assess the sustained tolerability and effects of NBM-DBS intervention in these PDD patients, as well as any possible impact on behavioral symptoms, quality of life, and caregiver burden and distress. Given the link between NBM cholinergic function, levels of behavioral arousal/attention and general cognitive performance, we hypothesize that baseline assessments of arousal/attention in PDD patients (serving as surrogate markers for residual NBM cholinergic integrity) could predict symptomatic response to NBM DBS. Specifically, we aimed to investigate whether baseline measurements of daytime sleepiness and accuracy on Posner's covert orienting of attention test can predict the cognitive status of patients after three years of continuous NBM-DBS therapy.

Methods

Patients

Six consecutive patients (all male) with a diagnosis of PDD according to the Movement Disorders Society Task Force on PDD[25,26] were treated with NBM-DBS at the National Hospital for Neurology and Neurosurgery from October 26, 2012 to July 31, 2015. Inclusion criteria were: diagnosis of PD and PDD, motor fluctuations, appropriate candidates for surgery, between the ages of 35–80, able to give informed consent, with a Mini-Mental State Examination (MMSE) score between 21 and 26, minimal atrophy on MRI, and living at home with a caregiver informant. Table 1 summarizes the baseline demographic and clinical characteristics of five of the six patients who participated in the current three-year follow-up study. The sixth patient died from causes unrelated to surgery after the 12 months follow-up, before the current 36 months follow-up.

DBS Surgery

The surgical procedure has been described previously[12] and involved bilateral DBS leads (model 3387 [patient A] or 3389 [patients B-F] Medtronic Inc.) implantation using a Leksell stereotactic frame under general anesthesia. Electrode implantation was guided by targeting the NBM on individual proton density 1.5 T MRI scans on which the internal globus pallidus (GPi), optic tract, anterior commissure, and adjacent NBM were visible. The deepest contacts were placed in the Ch4i because it has extensive cholinergic projections and the greatest possibility of successful electrode placement.[12] All devices were programmed with a frequency of 20 Hz and a pulse width of 60 μs, voltages selected were those producing the highest digit span scores with the lowest energy without adverse effects. Figure 1 and Table 2

TABLE 1 *Demographic and clinical characteristics*

ID	Age at surgery (years)	Gender	Disease duration at surgery (years)	Dementia duration at surgery (years)	Hoehn-Yahr stage at surgery
A	61	M	14	4	3
B	75	M	11	3	2
C	65	M	11	2	2
E	46	M	10	5	2
F	71	M	15	3	3
Mean	63.6		12.2	3.4	2.4
SD	11.2		2.2	1.1	0.5

shows stereotactic coordinates and location of the active NBM contacts and individual stimulation parameters.

Experimental Design

After surgery, patients were randomly assigned to 2 groups in a double-blind cross-over design: active stimulation or sham stimulation for 6 weeks. This period was followed by each group receiving the opposite "treatment' for another 6 weeks (details in Gratwicke et al, 2018[12]).

Follow-Up Assessment

The 6 patients were followed up 9 and 12 months after surgery. Details of the assessment battery have been previously reported.[12] In the present study, 5 patients were followed up 36 months after surgery.

Outcomes at 36 Months Follow-Up

At 36 months follow-up a short test battery was administered to minimize patient burden. The primary cognitive outcomes were changes on global cognition measured by the Mini Mental State Examination (MMSE)[27] (range 0–30) and Dementia Rating Scale-2 (DRS-2)[28] (range 0–144), administered and scored using standard procedures, with lower scores reflecting worse performance.

The following measures were used as secondary outcomes at 36 months to assess behavioral symptoms, quality of life, and caregiver burden:

The Blessed Dementia Scale (BDS)[29] was used to assess the general degree of functional change as reported by the caregiver (range 0 to 28) with higher scores indicating a greater loss of functional ability.

The Neuropsychiatric Inventory (NPI)[30] administered to the caregiver, assessed PDD-related behavioral disturbances and extent of caregiver distress for each domain, with higher score indicating more severe behavioral abnormalities. The frequency scale has scores ranging from 1 to 4 points (1 = rarely—less than once per week; 2 = sometimes—about once per week; 3 = often—several times per week but less than every day; 4 = very often—once or more per day). The severity scale has scores ranging from 1 to 3 points (1 = mild; 2 = moderate; and 3 = severe) and the scale for assessing caregiver distress has scores ranging from 0 to 5 points (0 = no distress; 1 = minimal distress; 2 = mild distress; 3 = moderate distress; 4 = severe distress; and 5 = extreme distress).

The Zarit Burden Interview (ZBI)[31] was administered to measure caregiver burden and distress. ZBI consists of 29 items to assess caregiver perception of burden as it affects their personal, social and financial wellbeing.

The Short Form-36 (SF-36)[32] was used as a measure of quality of life, with the caregiver as the proxy informant (range 0 to 100), higher scores indicating better health status in each of eight

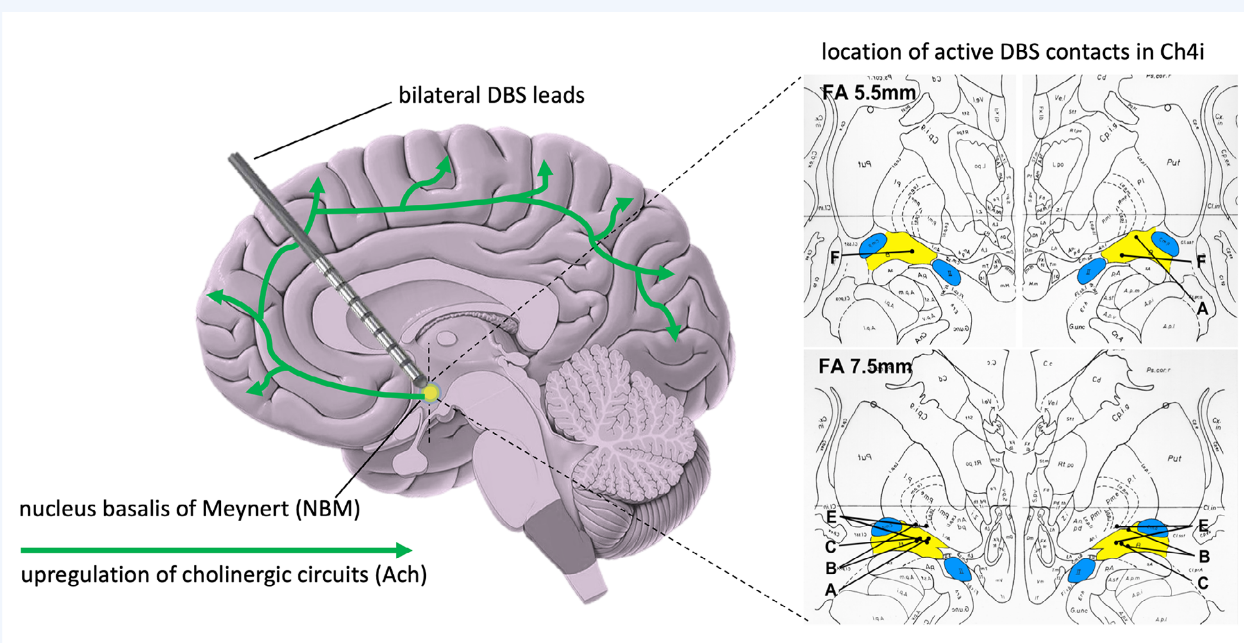

FIG. 1. Left: Deep brain stimulation of the nucleus basalis of Meynert (NBM) to promote residual cholinergic neuron activity for the upregulation of cortical acetylcholine (Ach) levels. Right: Active DBS contacts for all patients. The optic tract (II) and the lateral expansion of the anterior commissure are shown in light blue (cm.A). The NBM, which is shown in yellow, is located between these two structures and lower to the globus pallidus. In all patients, the most ventral active contact was implanted in the Ch4i subsector of NBM. Figure adapted from Schaltenbrand atlas (plates 25–26).

domains. The caregiver of patient F did not complete the SF-36 questionnaire at 36 months follow-up.

Baseline scores on the Posner covert orienting attention[23] and the daytime sleepiness item from the Scales for Outcomes in Parkinson's disease-Sleep (SCOPA-S)[33] were measured and subsequently used to determine whether they were associated with the cognitive outcome of NBM-DBS at 36 months follow-up.

Statistical Analysis

All data were analyzed using the computing environment R.[33] The yearly lost points from baseline to 9 months, 12 months, and 36 months, on the MMSE and DRS-2, was calculated. Pearson correlations were performed to explore the relationship between baseline measures and MMSE and DRS-2 at 36 months follow-up.

Results

The monitoring of adverse events showed that no serious adverse events occurred during the 36 months follow up period. During the 36 months follow up, 1 of the 6 trial participants had died after the 12 months follow-up, unrelated to surgery and one of the patients (A) was too cognitively impaired to complete the DRS-2.

Cognitive Outcome Measures at 36 Months Follow-Up

Changes in MMSE and DRS-2 scores over the follow up period are presented respectively in Table 3 and Table 4. All participants had dementia at baseline prior to surgery and follow-up data on the progression of dementia was available for all 5 participants. Patient A was only able to complete the MMSE at 36 months follow up and not the DRS-2 and did not complete the MMSE at 9 months follow up. The magnitude of change in MMSE and DRS-2 scores varied markedly between individual patients (Fig. 1). As evident from Figure 2, patients A, B, and F showed faster cognitive decline while patients C and E slower decline. For the MMSE (baseline median = 24, min-max = 21–25), the average annual loss of points at 36 months follow-up was −2.6, and the five patients varied between −0.3 and −5.4 MMSE points lost. For DRS-2 (baseline median = 116; min-max = 101–126), the average annual loss of points at 36 months was −10.3, and the patients varied between −0.7 and −17.9, consistent with some patients having stable global cognitive performance.

Behavioral Symptoms, Quality of Life and Caregiver Burden and Distress at 36 Months Follow-Up

The NPI, BDS, ZBI, and SF-36 were administered to the patients' caregivers and scores are presented in Tables 5 and 6.

TABLE 2 *DBS parameters and stereotactic coordinates*

ID	DBS intensity (V)	DBS pulse width (µs)	DBS frequency (Hz)	Stereotactics coordinates left	Stereotactics coordinates right	Active contacts
A	3.0	60	20	−17.6; 8.5; −6.1	19.3; 9.5; −4.8	0, 1, 8, 9
B	3.0	60	20	−19.0; 5.0; −2.9	18.5; 5.6; −3.8	0, 1, 8, 9
C	3.0	60	20	−19.0; 5.0; −3.8	17.9; 5.0; −3.9	0, 1, 8, 9
E	3.0	60	20	−22.2; 5.2; −5.2	20.2; 5.4; −6.2	0, 8
F	3.0	60	20	−20.8; 4.9; −6.4	19.7; 7.0; −5.5	0, 1, 8, 9

TABLE 3 *Changes in global cognition assessed by MMSE in Parkinson's disease dementia NBM-DBS*

	MMSE				Yearly lost points		
ID	Baseline	9 M	12 M	36 M	9 M	12 M	36 M
A	25	n.a.	22	12	n.a.	−3	−5.4
B	24	27	26	17	4	2	−2.6
C	25	21	21	24	−5.19	−4	−0.3
E	22	22	23	21	0	1	−0.3
F	21	18	12	12	−3.9	−9	−3.6
Median	24 (21/25)	21.5 (18/27)	22 (12/26)	17 (12/24)	−1.9 (−3.1/2.2)	−3 (−9/2)	−2.6 (−5.4/−0.3)

TABLE 4 *Changes in global cognition assessed by DRS-2 in Parkinson's disease dementia NBM-DBS*

	DRS-2				Yearly lost points		
ID	Baseline	9 M	12 M	36 M	9 M	12 M	36 M
A	124	122	117	n.a	−2.6	−7	n.a.
B	116	133	122	74	23.2	6	−16.1
C	126	119	113	124	−9.2	−13	−0.7
E	108	96	115	95	−15.7	7	−4.5
F	101	98	70	56	−3.9	−31	−18
Median	116 (101/126)	119 (96/133)	115 (70/122)	84.5 (56/124)	−3.9 (−9.2/23.2)	−7 (−31/7)	−10.3 (−18/−0.7)

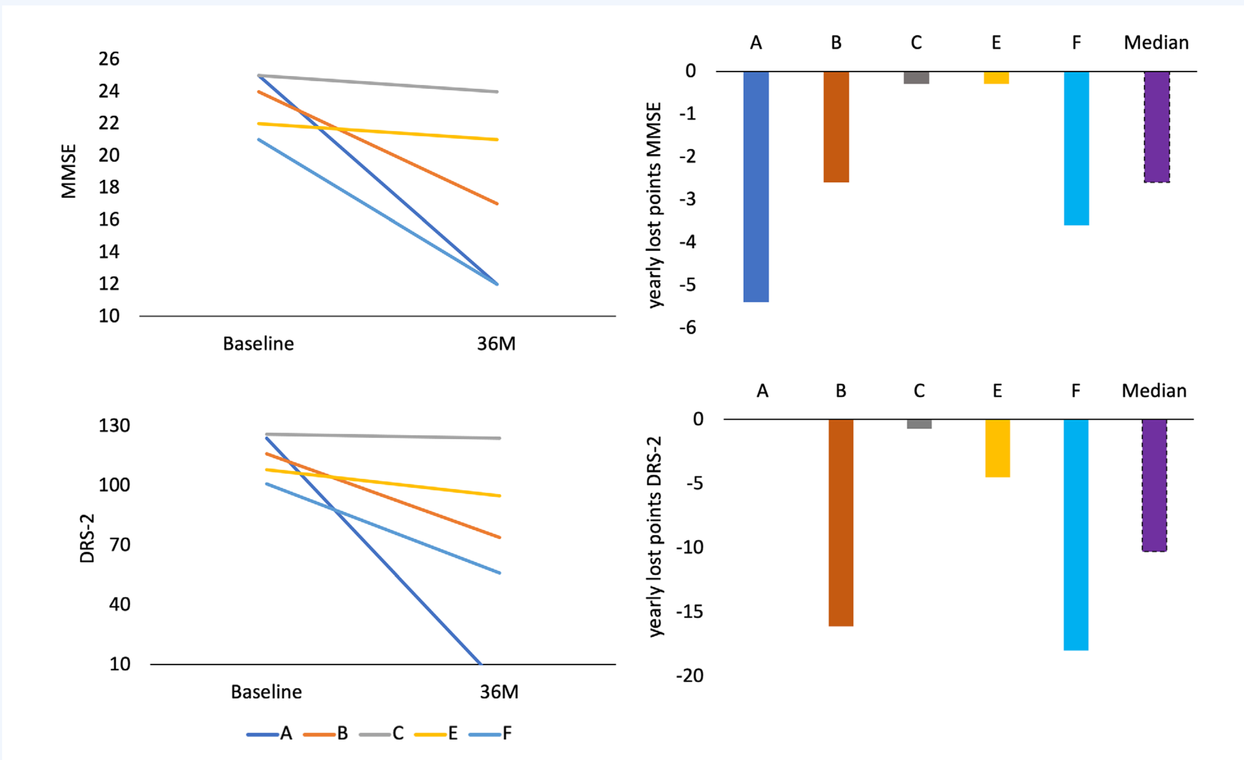

FIG. 2. Left: Individual trajectories of cognitive decline from baseline to 36 months follow up post nucleus basalis of Meynert deep brain stimulation, on mini mental state examination (MMSE) and dementia rating Scale-2 (DRS-2). Right: Bar plot showing the yearly lost points on MMSE and DRS-2 at 36 months follow up. Patient A did not complete the DRS-2 at 36 months follow up.

The caregiver of patient F did not complete the SF-36 questionnaire at 36 months follow-up.

At 36 months follow-up post NBM-DBS, caregivers of patients A and B reported an increase and the caregiver of patient C reported a reduction of behavioral disturbances assessed by the NPI total score. Importantly, patient C showed a reduction of visual hallucinations (from 2 to 0), patient E had no change, and patients A and B reportedly had an increase of NPI hallucination scores.

With regard to the subjective reporting of distress levels by the patients' caregivers on the NPI, the caregiver of patient B reported an increase in distress due to increased irritability and aggressive behavior of the patient (from 10 to 12). The caregiver of patient C also reported an increase of distress as a result of increase in the patient's score on the apathy subscale (from 0 to 3). The caregivers of patients A (from 7 to 3) and E (from 4 to 0) reported a reduction of caregiver distress.

In line with the relative slowing of cognitive decline, the reduction of behavioral disturbances and hallucinations, patient C also showed improvement on the BDS from severe to moderate deterioration (from 14 to 2.5) and patient E had a stable profile (from 8 to 9) on this scale.

The SF-36 median scores, maximum and minimum values on all dimensions are reported in Table 6: physical function (15, 0–80), role physical (65.5, 0–100), bodily pain (50, 12.5–75), general health perception (50, 20–55), vitality (43.7, 25–75), social

TABLE 5 *(A) Neuropsychiatric Inventory (NPI) at 36 months follow up; (B) Blessed Dementia Rating Scale pre-operatively and at 36 months follow up; (C) NPI caregivers burden pre-operatively and at 36 months follow up and Zarit caregivers burden at 36 months follow up; (D) pre-operative measures of Posner's covert orienting of attention task (% accuracy), and daytime sleepiness (the maximum SCOPA-S score is 18, with higher scores indicating greater sleepiness. The suggested cut-off score is 4 to 5)*

A

Neuropsychiatric Inventory (NPI)

ID	Delusion				Hallucination				Agitation aggression				Dysphoria depression				Anxiety				Euphoria elation			
	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C
A	n				y	1	2	0	n				y	1	1	3	n				n			
B	n				y	2	4	0	y	2	3	4	n				n				n			
C	n				n				n				n				n				n			
E	n				n				n				n				n				n			

ID	Apathy indifference				Disinhibition				Irritability lability				Aberrant motor				Night behavior				Appetite eating			
	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C	y/n	S	F	C
A	n				n				n				n				n				n			
B	n				n				y	2	1	4	y	2	4	4	n				n			
C	y	2	4	3	n				n				n				y	1	2	0	n			
E	n				n				n				n				n				n			

B

Blessed Dementia Rating Scale

ID	Baseline	36 M FU
A	9	12.5
B	10	9
C	14	2.5
E	8	9
F	13	n.a.
Median	10 (8/14)	9 (2.5/12.5)

C

NPI caregivers burden and Zarit caregivers burden

ID	Baseline	36 M FU	36 M FU
A	7	3	37
B	10	12	44
C	0	3	45
E	4	0	53
F	18	n.a.	n.a.
Median	7 (0/18)	3 (0/12)	44.5 (37/53)

D

pre-operative measures of Posner covert orienting of attention and SCOPA-S daytime sleepiness

ID	Posner %	Scopa-S
A	48	12
B	82	13
C	82	4
E	81	8
F	18	10
Median	81 (18/82)	10 (4/13)

Abbreviations: n.a., not assessed; n, absence of symptoms; y, presence of symptoms.

functioning (50, 25–75), role emotional (25, 0–83.3), mental health (52.5, 40–85).

Pre-Operative Predictors of NBM-DBS Cognitive Effects at 36 Months

Figure 3 shows the relation between the score on the Posner covert orienting of attention test and the SCOPA daytime sleepiness scale with the yearly loss of points on the MMSE and the DRS-2 at 36 months follow up. Variations in the Posner accuracy at baseline correlated positively and significantly with the numbers of points lost on the MMSE (r = 0.85, $P < 0.01$) and DRS-2 (r = 0.63, $P < 0.01$) at 36 months follow up. Patients A and F who presented with a low baseline Posner accuracy (A = 48, F = 48) rapidly and progressively deteriorated in terms of yearly lost points on the MMSE and DRS-2 (MMSE A = −5.4, F = −3.6; DRS-2 A = n.a, F = −18) over the 36-month follow-up period. By contrast, patients C and E showed high Posner accuracy at baseline (C = 82, E = 81) and stayed relatively cognitively stable, losing fewer points on the MMSE and DRS-2 (MMSE C = −0.3, E = −0.3; DRS-2 C = −0.7, E = −4.5) during the follow-up period over 36 months. Moreover, there was a relation between sleep quality at baseline and cognitive outcome at 36 months follow up. SCOPA sleepiness scale scores at baseline correlated negatively and significantly with the number of points lost on the MMSE (r = −0.75, $P < 0.01$) and the DRS-2 (r = −0.87, $P < 0.01$) at 36 months follow up. Patients A and F who presented more daytime sleepiness at baseline (A = 12, F = 13) rapidly lost points on the MMSE and the DRS-2 (MMSE A = −5.4, F = − 3.6) over the 36-month follow-up period. By contrast, patients C and E showed less daytime sleepiness at baseline (C = 4, E = 8) and stayed relatively cognitively stable losing fewer points on the MMSE and DRS-2 (MMSE C = −0.3, E = −0.3; DRS-2 C = −0.7, E = −4.5) during the 36 month follow-up period. These results are shown in Figure 3.

Discussion

The present study is a three-year (36 months) follow up of patients with PDD who underwent NBM-DBS with the aim of slowing down the progression of dementia. The primary goal was to evaluate the tolerability and effects of NBM-DBS on global cognition, behavioral symptoms, quality of life, and caregiver burden and distress. NBM-DBS was well tolerated during the course of the follow-up period with no major adverse effects or complications documented, supporting the safety of NBM-DBS in PDD.

We observed dissimilar trajectories of cognitive decline among the 5 patients over the 36 months follow-up period. There was a slower rate of progression of cognitive impairment in two of the five patients with PDD and NBM-DBS, while the others had a progressive worsening of symptoms despite NBM-DBS at the three years follow-up assessment. Specifically, patients A, B, and F had a rapid decline and progression of dementia, while patients C and E experienced a relatively slower disease progression at a rate that is typically unusual for this neurodegenerative disease. In fact, Aarsland and colleagues have documented that patients with PD who developed dementia have an annual mean decline of 2.3 points on the MMSE.[34] The annual loss points for patients C and E were 0.3 points consistent with a more stable global cognitive performance at 36 months assessment.

The relatively "stable" cognitive profile of these two patients during the follow-up provides some support for the hypothesis that stimulation of the NBM for an extended period might modulate remaining cholinergic transmission and ultimately have an impact on the rate of cognitive decline. This result is in line with the only previous evidence of NBM-DBS in PDD published by Freund and colleagues who showed an improvement of alertness and cognitive functionality during an open-label phase in one PDD patient.[11] However, in the absence of a control group of unoperated patients with PDD and evaluation of patterns of their cognitive decline over three years, the more "stable" cognitive profile of patients C and E cannot be directly attributed to NBM-DBS. This remains a task for future studies.

In our previous study[12] patients showed different clinical outcomes in response to NBM-DBS, highlighting the importance of a better understanding of pre-operative factors that might predict the outcomes of NBM-DBS. It is of utmost clinical importance to identify which patients are likely to benefit from NBM-DBS. On the basis of data which has associated lesions of the basal forebrain and cortical cholinergic projections to deficits of attentional functions,[35–38] we assessed whether baseline accuracy of covert attentional orienting could be predictive of better responsiveness to NBM-DBS. A previous investigation of NBM-DBS in Alzheimer's disease showed that patients with better baseline scores on the ADAS-cog had a relatively stable disease

TABLE 6 *Quality of life assessed by SF-36 in Parkinson's disease dementia NBM-DBS at 36 months followup*

SF-36	General health	Physical functioning	Physical role functioning	Emotional role functioning	Bodily pain	Social role functioning	Energy/fatigue	Emotional well-being
A	50	0	0	0	37.5	25	31.25	60
B	55	80	50	16.7	75	62.7	50	40
C	50	30	81.25	33.3	12.5	37.5	43.75	45
E	20	0	100	83.3	62.5	75	43.75	85
Median	50 (20/55)	15 (0/80)	65.6 (0/100)	25 (0/83.3)	50 (12.5/62.5)	50.1 (25/75)	43.75 (31.25/50)	52.5 (40/85)

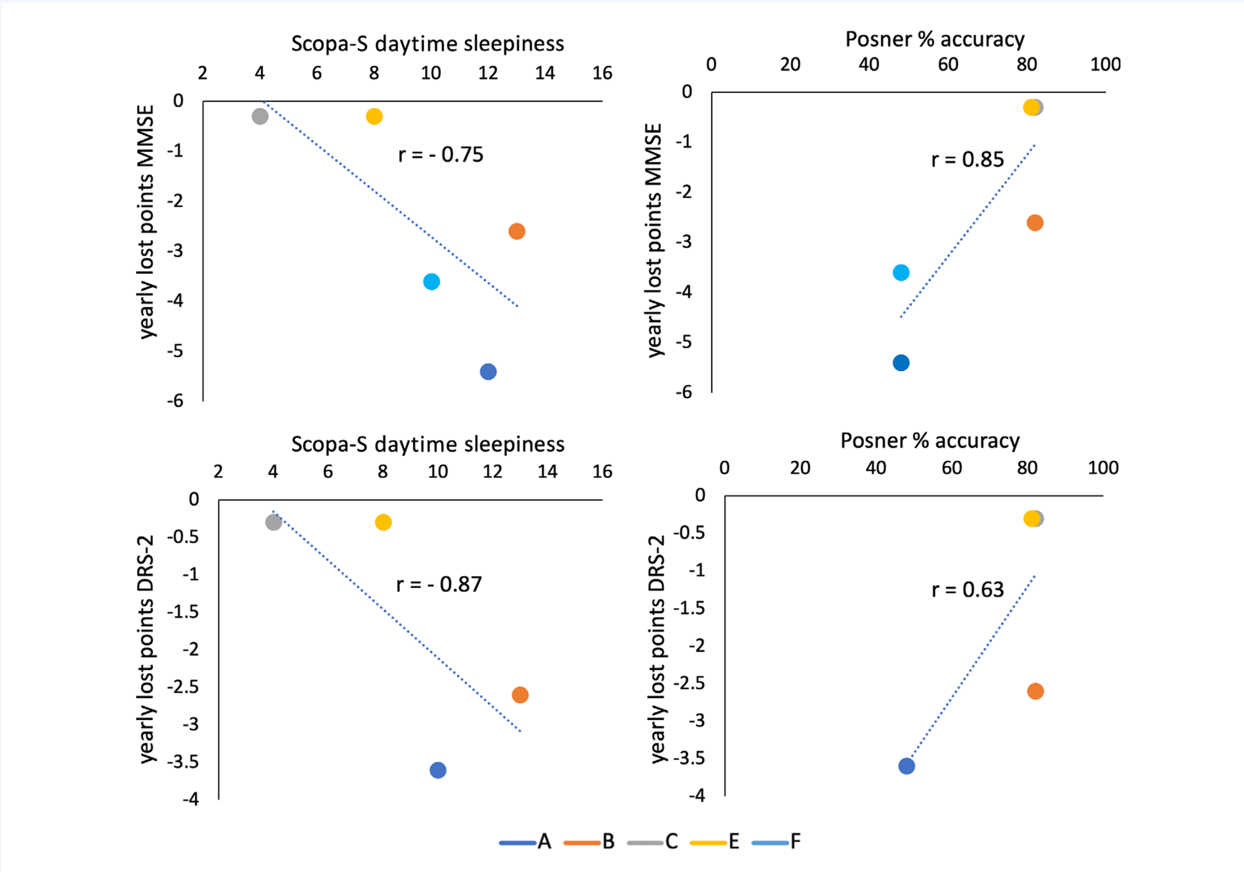

FIG. 3. Pearson correlations between Posner covert attention and SCOPA sleepiness scale pre-operative measures and the MMSE and DRS-2 at 36 months follow-up.

progression during the follow-up.[39] We found that patients with higher accuracy on the Posner test at baseline had a smaller reduction of points on the MMSE and the DRS-2 at the 36 month follow-up, suggesting that covert attentional orienting is predictive of a slower rate of cognitive decline in PDD who underwent NBM-DBS. Furthermore, we observed that patients C and E with less daytime sleepiness at baseline were those with a slower rate of cognitive decline. This is intriguing in light of evidence that the NBM has also been strongly linked to sleep/wake regulation. Thus, we can postulate that lower accuracy on the Posner test at baseline and excessive daytime sleepiness might indicate more widespread cholinergic degeneration and therefore less opportunity for NBM-DBS to activate residual neurons in the NBM. Our results linking excessive daytime sleepiness to a less favorable long-term NBM-DBS outcome are intriguing in light of evidence that sleep deterioration and excessive daytime sleepiness can accelerate the transition from mild cognitive impairment (MCI) to dementia and is strongly linked to PDD and AD pathogenesis by aggravating protein accumulation.[40] We also noted that the two patients (C and E) with a relatively better cognitive outcome at the 36 month follow-up were also relatively younger (C = 65, E = 46 years). Patient E had young onset dementia and was 46 years old at the time of surgery, with a ten-year illness duration and five-year history of dementia. This was significantly different than the other four patients, all of whom were operated on after the age of 60. We were unable to conduct genetic research for this study, but it would be fascinating to investigate the genetic profile of this patient, who does not fit the conventional PDD profile. These findings are in line with a previous study showing that surgical implantation of NBM-DBS in AD at an earlier stage of the disease and at a younger age have a favorable impact on disease progression and cognitive functions.[41] Overall, the different trajectory of decline in our patients is in line with prior NBM-DBS studies in AD and PDD that showed a noteworthy improvement in only a small number of the patients treated. Therefore, identifying reliable biomarkers that can predict the long-term benefit of NBM-DBS in dementia is one of the current major challenges. Despite the fact that our findings are limited in generalizability due to the small number of patients, it is tempting to suggest that the Posner task and daytime sleepiness, reflecting the residual functionality of NBM cholinergic fibers, may provide measures of the likelihood for NBM-DBS to be effective.

It is also worth noting that the optimal targeting and parameters of NBM-DBS for improving cognitive symptoms in dementia are currently based on limited evidence and are still under investigation. The rationale for using 20 Hz stimulation of the NBM is grounded on animal evidence showing that 20 Hz is the natural firing rate of NBM cholinergic neurons. NBM-DBS studies in PDD and AD have adopted continuous low frequency (e.g., 20 Hz) stimulation to boost the activity of residual cholinergic neurons. However, recent evidence in animal studies suggests that intermittent NBM-DBS is effective in improving working memory, whereas continuous stimulation was not.[42] Since different stimulation frequencies could have different impacts on neuronal networks, future studies modeling the electric field dynamics are encouraged to explore other stimulation protocols. Further, electrode lead implantation in the NBM might be complicated due to pathophysiological degenerative alterations (up to 70% cell loss in PDD) both in AD and PDD.[6] Baldermann and colleagues, in an attempt to characterize neuroimaging changes that are associated with the responsiveness to NBM-DBS in AD, showed that NBM-DBS is more useful in patients with less atrophy.[13]

The major limitation of our study is the small sample size and the lack of a control group of PDD patients who did not undergo NBM-DBS. The small sample size can be justified by the novelty of NBM-DBS for PDD. Similarly, given the novelty of this pilot study, inclusion of a non-operated control group was not feasible. There is a general lack of longitudinal studies of the progression of cognitive symptoms in PDD, but to overcome the limitation of not including an unoperated control group we compared MMSE score changes in our study with data showing the natural progression of PDD from Aarsland and colleagues.[34]

Despite these limitations, this study provides relevant information for future NBM-DBS studies. Current evidence suggests that candidates who are more likely to benefit from NBM-DBS are relatively younger patients, with a relatively well preserved covert attentional capacity and less daytime sleepiness. In conclusion, our longitudinal follow up of NBM-DBS in PDD adds to the existing evidence by showing that NBM-DBS is well tolerated over a period of three years, and suggesting that the inclusion of a comprehensive sleep assessment and Posner covert attention test may help as inclusion criteria for future clinical evaluation of NBM-DBS.

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Author Roles

(1) Research Project: A. Conception; B. Organization; C. Execution; (2) Experimental Procedures and Statistical Analysis: A. Design; B. Execution; C. Review and Critique; (3) Manuscript: A. Writing of the First Draft; B. Review and Critique.

D.C.: 1A, 1B, 1C, 2A, 2B, 2C, 3A,3B.
J.G.: 1A,1B, 1C, 2C, 3A, 3B.
L.Z.: 1C, 2C, 3A, 3B.
H.A.: 1C, 2C, 3B.
J.H: 1C, 2C, 3B.
M.H: 1C, 2C, 3B.
P.L: 1C, 2C, 3B.
T.F: 1A,1B, 1C, 2C, 3A, 3B.
M.J: 1A, 1B, 1C, 2A, 2C, 3A, 3B.

Disclosures

Ethical Compliance Statement: The trial conformed to the Seoul revision of the Declaration of Helsinki (2008) and Good Clinical Practice guidelines and was approved by the Queen Square National Hospital for Neurology and Neurosurgery local ethics Committee. All enrolled participants gave written informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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